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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/640,952	08/17/2000	Michael S. Kinch	3220-66872	3252

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

DATE MAILED: 12/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/640,952	KINCH ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *See Continuation Sheet* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) *92-96* is/are allowed.

6)☐ Claim(s) *See Continuation Sheet* is/are rejected.

7)☐ Claim(s) *50,54,77,81 and 98-101* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 3/24/03
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 69 has been canceled. Claims 1, 3-13, 21, 23, 24, 33, 36, 37, 41-47, 49-56, 59-68, 72, 73, 75-81, 90-101 are pending and under consideration.

2. After review and reconsideration, the Finality of the previous Office action is withdrawn in light of the rejections below.

3. Sections of Title 35, U.S. Code not found in this action can be found in a previous action.

4. Claims 21, 23 and 24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant method claims are dependent upon the identity of a "reagent capable of binding to a nucleic acid coding for EphA2 protein". The claims to not provide a structural limitation for said reagent. Thus the claims are dependent upon a genus of molecules which are described only by their function of binding to the nucleic acid encoding the protein. The art teaches that nucleic acids can hybridize to complementary nucleic acids. The specification teaches complementary nucleic acids which bind to the nucleic acids encoding EphA2. However the description of nucleic acids as reagents does not adequately describe the genus of reagents because said genus tolerates molecules which differ significantly in structure from a DNA or RNA, and would admit such entities as drug molecule not related in structure to the complement of the nucleic acid. One of skill in the art would reasonably conclude that applicant was not in possession of the claimed genus of reagents. It follows logically that if applicant was not in possession of the product on which a method claim relies, than applicant was not in possession of the claimed method..

5. Claims 1, 3-8, 10, 11, 13, 33, 36, 37, 41, 42, 45, 47, 49, 55, 56, 59-65, 68, 72, 73, 75, 76, 78, 79, 80, 90, 91 and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Zantek et al (Molecular Biology of the Cell, Nov 1998, Vol. 9, suppl., page 134A,

reference of the IDS submitted Feb 12, 2001) as evidenced by the abstract of Chen et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 24670-24675, cited in a previous Office action) in view of Larrick et al (In: Human Hybridomas and Monoclonal Antibodies, Engleman and Foung, Ed.s, 1985, pp. 8-9, cited in a previous Office action) and Campbell (Monoclonal Antibody Technology, 1985, pages 1-32) and Lindberg et al (Molecular and Cellular Biology, 1990, Vol. 10, pp. 6316-6316, cited in a previous Office action).

The abstract of Chen et al discloses that EphA2 is synonymous with Eck.

The abstract of Zantek et al teaches that ECK expression and post-translational modifications distinguished three stages of breast cancer progression: 1) normal breast epithelium expressed tyrosine phosphorylated ECK enriched in cell-to-cell contacts; 2) poorly invasive cells lost ECK expression; and 3) metastatic cells expressed non-phosphorylated ECK at membrane ruffles. The abstract teaches that ECK is important in breast cancer progression and ECK may be used as a diagnostic marker. The abstract does not teach a monoclonal antibody which specifically binds to ECK.

Lindberg et al teach the tyrosine residue which is a phosphorylation site within ECK, wherein said tyrosine is an intracellular tyrosine (residue 772. Figure 1).

Larrick et al teach the advantages of using a monoclonal antibody over a polyclonal antibody which include a constant propagating source (pages 7-8, under the heading IV).

Campbell teaches that it is routine to make antibodies to proteins of interest.

It would have been prima facie obvious at the time the claimed invention was made to detect unphosphorylated ECK as a marker for metastatic breast cancer by a monoclonal antibody that specifically bound to unphosphorylated ECK at the epitope including tyrosine 772. It would also have been obvious to detect phosphorylated ECK as a marker for normal breast cancer cells. One of skill in the art would have been motivated to do so by the general teachings of Campbell and Larrick et la regarding the advantages of using monoclonal antibodies to proteins, and the specific teaching of Lindberg et al regarding the phosphorylation site of ECK. One of skill in the art would be motivated to make a monoclonal antibody that bound specifically to ECK which was unphosphorylated at position 772 in order to discern metastatic melanoma cells from normal cells. One of skill in the art would be motivated to make a monoclonal antibody that bound specifically to ECK which was unphosphorylated at position 772 in order to discern normal

breast cancer cells from cancerous breast cancer cells. Lysing the cells would be further obvious in order to have access to the intracellular epitope comprising the tyrosine 772.

6. Claims 1, 3-8, 10-13, 33, 36, 37, 41, 42, 45-47, 49, 55, 56, 59-65, 68, 72, 73, 75, 76, 78, 79, 80, 90, 91 and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Zantek et al, the abstract of Chen et al, Larrick et al, Campbell and Lindberg et al as applied to claims 1, 3-8, 10, 11, 13, 33, 36, 37, 41, 42, 45, 47, 49, 55, 56, 59-65, 68, 72, 73, 75, 76, 78, 79, 80, 90, 91 and 97 above, and further in view of Pendergast et al (WO 97/15587).

The combination of references does not specifically teach using a second antibody having phosphotyrosine specificity in a Western Blot.

It is recognized in the art that antiphosphotyrosine antibodies can be used in Western Blotting in order to determine the phosphorylation state of a protein, as exemplified by Pendergast et al (page 27, lines 8-12).

It would have been prima facie obvious at the time the claimed invention was made to provide an assay for the detection of the phosphorylated ECK versus no phosphorylated ECK by Western blotting in the method rendered obvious by the combination of .....
One of skill in the art would have been motivated to do so by the what is well known in the art as exemplified by the teachings of Pendergast et al,

7. Claims 1, 3-11, 13, 33, 36, 37, 41-45, 47, 49, 55, 56, 59-68, 72, 73, 75, 76, 78, 79, 80, 90, 91 and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Zantek et al, the abstract of Chen et al, Larrick et al, Campbell and Lindberg et al as applied to claims 1, 3-8, 10, 11, 13, 33, 36, 37, 41, 42, 45, 47, 49, 55, 56, 59-65, 68, 72, 73, 75, 76, 78, 79, 80, 90, 91 and 97 above, and further in view of the abstract of Terstappen et al (Vox Sanguinis, 1998, 74 suppl. 2, pp. 269-274).

The abstract of Terstappen et al teaches that circulating breast cancer cells can be found in the blood and that the level of cells detected differ significantly between patients in whom the tumor is confined to the primary site versus patients with metastatic disease.

It would have been prima facie obvious at the time the claimed invention was made to detect ECK in breast cancer cells isolated from the peripheral blood. One of skill in the art

would have been motivated to do so by the teachings of the abstract of Terstappen et al on the correlation between the progression of breast cancer and the presence of circulating breast cancer tumor cells in the blood.

8. Claims 47, 51-53, 55, 56, 59-65, 68 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Zantek et al (Molecular Biology of the Cell, Nov 1998, Vol. 9, suppl., page 134A) as evidenced by the abstract of Chen et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 24670-24675, cited in a previous Office action) in view of Larrick et al (In: Human Hybridomas and Monoclonal Antibodies, Engleman and Foung, Ed.s, 1985, pp. 8-9, cited in a previous Office action) and Campbell (Monoclonal Antibody Technology, 1985, pp. 1-32).

The abstract of Zantek et al teaches that ECK expression and post-translational modifications distinguished three stages of breast cancer progression: 1) normal breast epithelium expressed tyrosine phosphorylated ECK enriched in cell-to-cell contacts; 2) poorly invasive cells lost ECK expression; and 3) metastatic cells expressed non-phosphorylated ECK at membrane ruffles. The abstract teaches that ECK is important in breast cancer progression and ECK may be used as a diagnostic marker. The abstract does not teach a monoclonal antibody which specifically binds to ECK.

Larrick et al teach the advantages of using a monoclonal antibody over a polyclonal antibody which include a constant propagating source (pages 7-8, under the heading IV).

Campbell teaches that it is routine to make antibodies to proteins of interest.

It would have been prima facie obvious at the time the claimed invention was made to detect extracellular ECK on the membrane ruffles of metastatic cells by binding of an ECK specific antibody. One of skill in the art would have been motivated to do so by the suggestion of the abstract of Zantek on the expression of ECK on the membrane ruffles of metastatic breast cancer cells. One of skill in the art would have been motivated to make the monoclonal antibody by the teachings of Larrick et al and Campbell regarding the advantages associated with monoclonal antibodies. One of skill in the art would be motivated to have the monoclonal antibody which binds to the extracellular portion of ECK at membrane ruffles in order to stain tissue samples and observe the localization of cell expressing ECK within said sample.

9. Claims 21 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Zantek et al (Molecular Biology of the Cell, Nov 1998, Vol. 9, suppl., page 134A) as evidenced by the abstract of Chen et al (Journal of Biological Chemistry, 1998, Vol. 273, pp. 24670-24675, cited in a previous Office action) in view of Lindberg et al (Molecular and Cellular Biology, 1990, Vol. 10, pp. 6316-6316, cited in a previous Office action) and Hoon et al (US 6,057,105).

The abstract of Zantek et al teaches that ECK expression and post-translational modifications distinguished three stages of breast cancer progression: 1) normal breast epithelium expressed tyrosine phosphorylated ECK enriched in cell-to-cell contacts; 2) poorly invasive cells lost ECK expression; and 3) metastatic cells expressed non-phosphorylated ECK at membrane ruffles. The abstract teaches that ECK is important in breast cancer progression and ECK may be used as a diagnostic marker. The abstract does not teach the detection of metastatic cancer comprising the detection of ECK nucleic acids.

Lindberg et al teach that ECK is an epithelial cell receptor protein (title) and is expressed at highest levels in the lung, skin, ovary and small intestine (page 6323, second column, lines 37-38).

Hoon et al teach a method of detecting metastatic breast cancer cells comprising isolating nucleic acids from a sample taken from a patient and detecting the presence of nucleic acids from cancer marker genes, wherein the biological sample is from a compartment in which normal cells are negative for the breast cancer marker genes (claims 39 and 42). Hoon et al teach that the sample is blood, tumor draining lymph node, bone marrow and CSF.

It would have been prima facie obvious at the time the claimed invention was made to isolate nucleic acids from a sample of bone marrow, tumor draining lymph node, blood or CSF taken from a patient and determine the expression of ECK. One of skill in the art would have been motivated to do so by the teachings of Zantek et al on the expression of ECK in metastatic cells and the teachings of Hoon et al on the ability to detect metastatic cells expressing a cancer marker protein among a population of cells which do not express said protein and the teaching of Lindberg et al on the expression of ECK in lung, skin, ovary and small intestine. One of skill in the art would understand that blood, bone marrow and lymph cells would not express ECK as

said cells were hematopoietic cells rather than epithelial cells . One of skill in the art would also understand that CSF would also not be a source for an epithelial cell marker in an normal individual.

10. Claims 21, 23 and 24 rejected under 35 U.S.C. 103(a) as being unpatentable over the abstract of Zantek et al, the abstract of Chen et al, Lindberg et al and Hoon et al as applied to claims 21 and 23 above, and further in view of Wittwer et al (US 6,174,670).

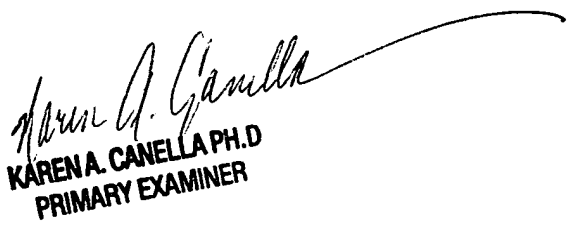
The combination does not teach the detection of the reagent nucleic acid binding. Wittwer et al teach an improved method of amplifying a target nucleic acid sequence biological sample, said method comprising the steps of (a) adding to the biological sample an effective amount of a nucleic-acid-binding fluorescent entity; (b) amplifying the target nucleic acid sequence using polymerase chain reaction, comprising thermally cycling the biological sample using initial predetermined temperature and time parameters, and then (i) illuminating the biological sample with a selected wavelength of light that is absorbed by said fluorescent entity during the polymerase chain reaction; (ii) monitoring fluorescence from said sample to determine the optimal temperature and time parameters for the polymerase chain reaction; and (iii) adjusting the initial temperature and time parameters in accordance with the fluorescence, wherein the monitoring fluorescence step consists of monitoring an amplification dependent emission of the fluorescent entity.

It would have been prima facie obvious at the time the invention was made to use the method taught by Wittwer et al to detect nucleic acid hybridization resulting from the PCR amplification of the target cancer gene of ECK. One of skill in the art would have been motivated to do so by the teachings of Wittwer et al on the improvement of being able to detect the hybridization product in a very short time.

11. Claims 50, 54, 77, 81 and 98-101 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (571) 272 0828. The examiner can normally be reached on Monday, Tuesday and Thursday from 10:00 am to 8 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, can be reached on (571) 272 0832. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308 0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1643



Continuation of Disposition of Claims: Claims pending in the application are 1,3-13,21,23,24,33,36,37,41-47,49-56,59-68,72,73,75-81 and 90-101.

Continuation of Disposition of Claims: Claims rejected are 1,3-13,21,23,24,33,36,37,41-47,49,51-53,55,56,59-65,68,72,73,75,76,78-80,90,91 and 97.